

# Comparison of High Sensitivity C Reactive Protein in subject with normal and low ankle brachial index

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## ABSTRACT

**Objective:** To compare high sensitivity C reactive protein in subjects with normal and low ankle brachial index.

**Methods:** In a cross sectional observational study, 150 subjects were selected from either sex with age more than 45 years for males and 50 years for females along with conventional cardiovascular risk factors including hypertension, obesity, smoking and diabetes. The subjects were divided on the basis of basis of ABI >0.9 and <0.9 into two groups. The subjects were measured for BMI, lipid profile, serum glucose and hs CRP. ABI was taken from subjects in supine position after rest of 10 min by using hand held Doppler.

**Results:** The levels of hs-CRP were significantly higher in group with low ABI <0.9 as compared to group with normal ABI >0.9 (p value is <0.001). A significant and positive correlation of both ABI and hs-CRP was observed with systolic blood pressure and pulse pressure. The correlation was non significant with diastolic blood pressure. The Pearson regression analysis showed significant negative correlation between hs-CRP and ABI.

**Conclusions:** In our study we found negative correlation of ABI and hs-CRP which confirms the role inflammation in atherosclerosis. hs-CRP add predictive power to traditional factors for risk individuals.

**Keywords:** C-reactive protein, ankle brachial index

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## INTRODUCTION

The vast majority of cardiovascular and cerebrovascular events occur in the healthy population, with only 20% occurring in subjects with preexisting clinical disease. A major public health challenge is therefore to accurately identify, in an apparently healthy population, those who are at high risk and to target prevention at these individuals<sup>1</sup>.

Therefore, non-invasive tests to detect individuals with atherosclerosis, preferably before they develop ischemic cardiovascular disease, may improve selection of individuals for preventive treatments. In this context, the importance of the early identification and treatment of peripheral arterial disease (PAD) has been increasingly acknowledged recently<sup>2</sup>. Reduction of systolic blood pressure at ankle level, caused by peripheral arterial disease can detect atherosclerosis non-invasively even in asymptomatic individuals and identified as reduced ankle brachial index (ABI). Similarly another test that can potentially detect atherosclerosis non-invasively is C reactive protein, recommended by American Heart Association in risk assessment of primary prevention of cardiovascular disease. This is because inflammation is an important part of atherosclerosis<sup>3</sup>. PAD is very thrombogenic and consists of large percentage of diabetics, hyperlipidemics and smokers,

conditions all associated with endothelial dysfunction and a hypercoagulable state<sup>4</sup>. Also individuals with PAD have a heightened inflammatory state similar to individuals with unstable angina. Additionally, some studies have reported links between newer (novel) cardiovascular markers and PAD. Especially homocysteine, C reactive protein, IL6, fibrinogen D-dimer, plasma anti plasmin complex have been reported to be linked with PAD<sup>5</sup>.

Hypertension is also positively associated with PAD as shown in the National Health and Nutrition Survey. Hypertension is present in one third of the patients with peripheral arterial obstructive disease (PAOD). In a research, Binaghi et al<sup>6</sup> have shown that the predominance of hypertension in patients with PAOD is 21.6%, second only to hypercholesterolemia (59.1%). Hypertension is related to the risk of premature atherosclerosis risk, independently from other major risk factors.

C reactive protein is established marker of low grade inflammation, reflecting elevated levels of proinflammatory cytokines such as interleukin 6. It can be measured in serum with high sensitive, cost effective and standardized assays. High sensitive CRP (hs-CRP) measure gradations of CRP previously considered within normal range. The highest quartile of hs-CRP at base line had a 4 fold higher risk of severe PAD<sup>7</sup>.

The InCHIANTI study<sup>8</sup> and the recent NHANES<sup>9</sup> found significant associations between CRP and prevalence of ABI<0.9.

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CRP is the major acute phase protein in human. It has proven to be an independent marker of the extent of atherosclerosis in coronary, cardiovascular and PAD. During recent years, the importance of CRP and its measurement in the laboratory has dramatically changed. Renewed interest in CRP emerged when it was reported that deaths arising from heart disease declined, yet up to one half of all myocardial infarction occur in healthy men and women with normal plasma lipid<sup>10</sup>.

**SUBJECTS AND METHODS**

This study was carried out in the Department of Physiology, Basic Medical Sciences Institute, and Jinnah Postgraduate Medical Centre Karachi with collaboration of Department of Medicine Abbassi Shaheed Hospital and Jinnah Post Graduate Medical Centre Karachi from Jan-Mar 2009. This was cross sectional, descriptive, observational study, involved no therapeutic interventions, performed on 150 out patients. Subjects were divided on the basis of ABI >0.9 and ABI<0.9 into two groups and compared different variables. Participating individuals was selected on the basis of age, sex, & the presence of conventional cardiovascular risk factors: hypertension, obesity, smoking, diabetes, hypercholesterolemia, decreased HDL cholesterol and family history of early cardiovascular disease.

Hs CRP was done by Enzyme Immunoassay test by Kit method, Cat No. BC-1119 by BioCheck, Inc. The hand held pocket Doppler with 8 MHz probe (Sonotrax Vascular, Edan Instrument, Inc. Serial No.STAV0840563) and mercury sphygmomanometer was used to calculate ABI. Specifically the inclusion criteria were for men 1. Age >45 yrs with one or more risk factors. 2. Age >65 yrs. 3. Individuals with NIDDM

For women: 1. Age > 50 yrs with one or more risk factors. 2. Age > 65 yrs.

3. Individuals with NIDDM

C) Family history of early coronary heart disease.

**Exclusion criteria:**

- Patients who had prior evidence of atherosclerotic lesion.
- Contra-indication of ABI measurement which includes painful inflammatory processes, wounds, phlebitis, extreme edema, If ABI >1.4 this indicate incompressible vessels.
- Hyperthyroidism.
- Uncontrolled neoplastic disease.
- Any acute inflammatory condition

**Statistical analysis:** Data analysis was performed using SPSS version 10.0. All continuous response variables like age, weight, fasting blood sugar were presented by mean ± SD; Students t-test (unpaired) was applied to compare means of these variables

between two groups. The results were considered statistically significant if  $p \leq 0.05$  and it was taken as highly significant if P-value was less than 0.001.

**RESULTS**

Table 1 is showing comparison of hs C-reactive protein in subjects with ABI >0.9 (group I) and <0.9 (group II). It was observed that levels of hs-CRP were significantly higher in group II as compared to group I and p value is <0.001. Figure 1 is showing significant negative correlation of ABI with hs CRP.

Table 2 is showing correlation coefficient of Ankle brachial index and hs-CRP with variable; Systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure. A significant and positive correlation of both ABI and hs-CRP was observed with SBP and pulse pressure. The correlation was non significant with DBP.

Table 1: Comparison of high sensitivity c reactive protein on the basis of ABI>0.9 (Group I) and <0.9(Group II)

Variables	Group I ABI>0.9 Mean ± SEM	Group II ABI<0.9 Mean ± SEM
Hs-CRP	2.9 ± 0.16	4.5 ± 0.33

P value: 0.001\*\*

\*\*p value is highly significant at the 0.001 level

Fig. 1: Correlation coefficient of ankle brachial index vs high sensitivity C- reactive protein

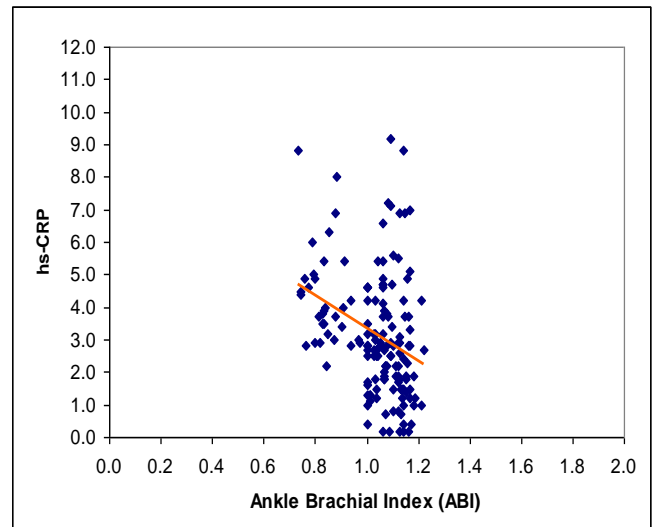


Table 2: Correlation coefficient of ankle brachial index and HS-CRP vs systolic BP, diastolic BP and pulse pressure

Correlation Coefficient	ABI index	hs-CRP
SBP Pearson correlation	$r = -0.33^{**}$	$r = 0.34^{**}$
p-value	0.01	0.01
DBP Pearson correlation	$r = 0.03$	$r = 0.12$
p-value	0.76	0.15
Pulse pressure-Pearson correlation	$r = -0.39^{**}$	$r = 0.33^{**}$
p-value	0.01	0.01

\*Correlation is significant at the 0.05 level (2 tailed)

\*\*Correlation is significant at the 0.01 level (2 tailed)

## DISCUSSION

As inflammation is involved in atherosclerosis, it was expected that individuals with reduced ABI, as sign of atherosclerosis in leg, should have increased C reactive protein, exactly as we observed. It is worth noting that our results suggest an inverse relationship between high sensitivity CRP and ABI supporting the existence of a link between atherosclerosis and inflammation. These findings were in agreement with the large population cohort studies, the Edinburgh artery study<sup>11</sup> and Rotterdam study<sup>12</sup>.

Wildman et al<sup>9</sup> also found CRP level related to PAD (ABI <0.9) in a cross sectional sample of US adult population. More over high levels were associated with increased severity of PAD in Edinburgh artery study. Furthermore, McDormatt et al<sup>13</sup> found that elevated CRP levels were associated with decreased functional capacity of individuals with PAD.

As expected in our study, systolic blood pressure was inversely related to ABI. There was also significant difference in pulse pressure of normal and low ABI index groups. And we have found inverse relation of pulse pressure with ABI. In respect to SBP and pulse pressure, our results agreed with Hasimu et al<sup>14</sup> and Gabriel et al.<sup>15</sup>, thus highlighting the role of these risk factors in the development of atherosclerotic processes in distinct vascular territories, as well as confirming concomitance of risk factors both in coronary artery disease and PAD

In our study hs-CRP has been more strongly associated with systolic BP than diastolic BP which is consistent with the emerging importance of systolic blood pressure as a mean of cardiovascular risk prediction. This finding was in agreement with Rohde et al<sup>16</sup>, Sesso et al<sup>17</sup>, Bermudez et al<sup>18</sup>. In the study done by Ryu et al<sup>19</sup>, diastolic BP pressure was more strongly correlated with CRP than with systolic BP.

## CONCLUSION

Negative correlation of ABI and hsCRP confirms the role of inflammation in atherosclerosis. Hs CRP add predictive power to traditional risk factors. The screening for atherosclerosis might be useful.

## REFERENCES

1. Lee AJ, Price JF, Russell BA. Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors: The Edinburgh Artery Study. *Circulation* 2004;110:3075.
2. Ogren M, Hedblad B, Engstrom G. Prevalence and prognostic significance of asymptomatic peripheral

- arterial disease in 68 yrs old men with diabetes. *Eur J Vasc Endovasc Surg* 2005; 29:182-189.
3. American Heart Association, Human Blood Pressure determination by Sphygmomanometry; 2001.
4. Shammass NW, Dippel EJ. Evidence-based management of peripheral vascular disease. *Curr Atheroscler Rep* 2005; 7: 358-63.
5. Rassoul F, Richter V et al. Plasma homocysteine and lipoprotein profile in patients with peripheral arterial occlusive disease. *Angiology* 2000; 51:189-196
6. Binaghi F, Fronteddu PF, Cannas F, Caredda E et al. Prevalence of arterial occlusive disease and associated risk factor in a sample of southern Sardinian population. *Int Angiol.* 1994; 13(3): 235-245.
7. Pearson TA. New tools for Coronary risk assessment: what are their advantages and limitations? *Circulation* 2002; 105; 886-892.
8. McDermott MM et al. Patterns of inflammation associated with peripheral arterial disease: the InCHIANTI study. *Am Heart J.*2005;150: 276 -281.
9. Wildman RP, Muntner P, Chen J. Relation of inflammation to peripheral arterial disease in the national health and nutrition examination survey, 1999-2002. *Am J Cardiol* 2005; 96:1579-1583.
10. Amore JD. Evaluation of C-reactive protein as a cardiac risk factor. *Lab. Medicine* 2005;36(4): 234-238.
11. Tzoulaki I, Murray GD, Lee AJ, Rumley A, Lowe GD. C-reactive protein, interleukin-6, and soluble adhesion molecules as predictors of progressive peripheral atherosclerosis in the general population: Edinburgh Artery Study. *Circulation.* 2005; 112: 976-983.
12. Van der Meer IM, de Maat MP et al. Inflammatory mediators and cell adhesion molecules as indicators of severity of atherosclerosis: the Rotterdam study. *Arterioscler Thromb Vasc Biol.* 2002; 22:838-842.
13. McDermott MM, Greenland P, Liu K et al. The ankle brachial index is associated with leg function and physical activity: the walking and leg circulation study. *Ann Intern Med* 2002; 136: 873-883.
14. Hasimu B, Li j, Nakayama t Yu J. Ankle brachial index as a marker of atherosclerosis in Chinese pts with high cardiovascular risk. *Hypertens Res* 2006;29(1) :23 -27.
15. Gabriel SA, Serafim PH, Freitas CE, Tristao CK,. Peripheral arterial occlusive disease and ankle brachial index in patients who had coronary angiography. *Braz J Cardiovasc Surg* 2007; 22 (1): 49.
16. Rohde LE, Hennekens CH, Ridker PM. Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. *Am J Cardiol* 1999; 84: 1018.
17. Sesso HD, Bruing JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. *JAMA* 2003; 290: 2945-51.
18. Bermudez EA, Rifai N, Buring J. Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. *Arterioscler Thromb Vasc Biol* 2002; 22: 1668-73.
19. Ryu SY, Lee YS. Relations of Plasma High-Sensitivity C-Reactive Protein to Various Cardiovascular Risk Factors. *J Korean Med Sci* 2005; 20: 379-83.